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PREPARATION OF CHIRAL PYRROLE DERIVATIVES BY THE PAAL-KNORR REACTION

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A new approach has been developed for the synthesis of N-alkylpyrroles with a chiral substituent at the nitrogen atom by the Paal-Knorr reaction using esters of amino acids as the source of chirality.

Keywords: 1,4-dicarbonyl compounds, 2,5-dimethyl- and 5-aryl-2-methylpyrroles with a chiral substituent at the nitrogen atom, chiral pyrrole derivatives, iodine-catalyzed cyclization, Paal-Knorr method, Stetter reaction.

Modern researchs in chemistry of pyrrole and its derivatives are aimed at finding new pathways for the synthesis of natural compounds containing a pyrrole fragment. This heterocyclic system holds interest since pyrrole derivatives are a component part of many natural compounds such as vitamin B12, bile pigments, heme, chlorophyll, alkaloids lukianol, (+)-dragmacidin F, lamellarin, rhazinilam, roseophilin and others [1]. A number of synthetic compounds containing the pyrrole fragment display biological activity [2] such as antimicrobial, antiviral [3], and antitumor action, effects on the central nervous system, and participation in metabolism. Well-known drugs derived from pyrrole such as Ketorolac and Atorvastatin are used in medicine. Pyrroles and their derivatives are used as dyes, analytical reagents, catalysts, and protective groups [1].

There is increasing interest in organic, medical, and pharmaceutical chemistry in the search for synthetic pathways to chiral structures. This interest has arisen in light of the direct dependence of the biological activity of chiral organic compounds on their absolute configuration. This phenomenon is encountered for pyrrole derivatives containing a chiral substituent at the nitrogen atom, which are potential building blocks for the synthesis of biologically active compounds with an optimal combination of activity and safety.

Two principal approaches may be proposed for the synthesis of pyrroles with a chiral substituent at the nitrogen atom: 1) direct alkylation of pyrroles with chiral alkylating reagents and 2) formation of the pyrrole ring using chiral acyclic precursors.

The N-alkylation of pyrroles requires the prior generation of the pyrrolyl anion bound to a metal cation by an ionic bond. Thus, for example, alkylation of esters of chiral α-hydroxy acids by tosylates is carried out in polar aprotic solvents such as DMF and acetonitrile by the action of bases [5]. The alkylation proceeds at room temperature and complete conversion is achieved after only 1 h with ~75% yield [6]. However, this method is

Dedicated to L. I. Belen'kii on the occasion of his eightieth birthday.

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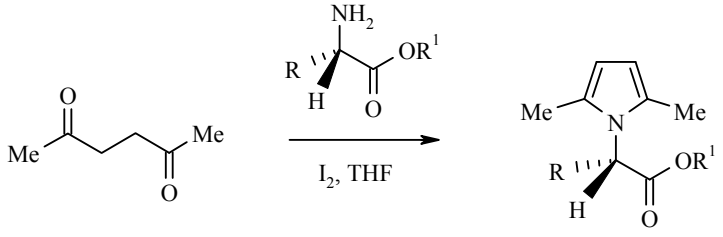
clearly unsuitable for pyrroles with a chiral substituent at the nitrogen atom since the use of basic media may lead to racemization due to the CH acidity of the chiral site. Such racemization is seen in the basic hydrolysis of esters of α-amino acids [7].

Thus, it is clearly necessary to use the second approach to the synthesis of pyrroles with a chiral substituent at the nitrogen atom involving Paal-Knorr cyclization using chiral amines since the chiral site in this case is not affected in the reaction.

There are quite a few methods for carrying out the Paal-Knorr condensation of 1,4-dicarbonyl compounds with amines [8-10]. Special interest is found in cyclization in the presence of iodine [11], which significantly enhances the efficiency of the reaction due to activation of the carbonyl compound through formation of complexes with iodine acting as a Lewis acid [12].

We used this method for the synthesis of chiral derivatives of N-alkyl-2,5-dimethylpyrroles employing acetonylacetone and esters of optically active α-amino acids as the amine component. The reaction was carried out in THF in the presence of catalytic amounts of iodine. This procedure permitted us to obtain pyrroles with a chiral substituent at the nitrogen atom in high synthetic and enantiomeric yields.



1a–e

1 a R = Me, R^1 = Et; **b** R = Me, R^1 = *t*-Bu; **c** R = *i*-Pr, R^1 = Et;
d R = CH_2Ph, R^1 = Et; **e** R = CH_2Ph, R^1 = *t*-Bu

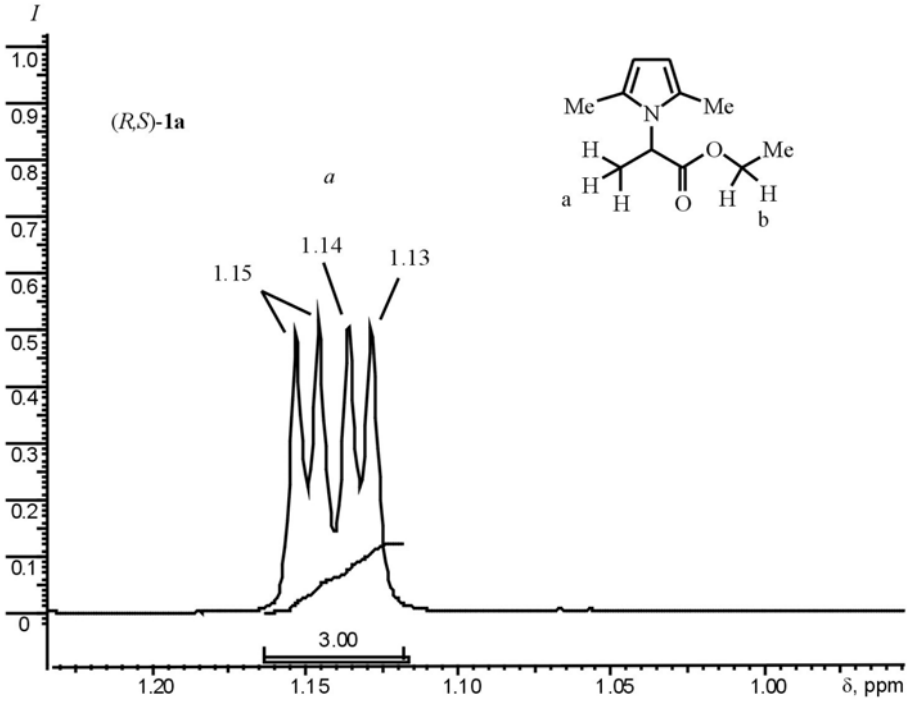
The ^{1}H NMR spectra of (*R,S*)-**1a** and (*S*)-**1a*** were taken in the presence of an equimolar amount of chiral solvating agent (*S*)-1,1'-binaphthyl-2,2'-diol to determine the optical purity of the esters of (*S*)-N-alkylpyrroles **1**. The chiral solvating agent, (*S*)-1,1'-binaphthyl-2,2'-diol, is commonly used to determine the enantiomeric purity of esters of carboxylic acids, amines, and some other compounds [13]. The action of this reagent has been related to solvation due to hydrogen bonding between the two hydroxyl groups of (*S*)-1,1'-binaphthyl-2,2'-diol and the carbonyl group oxygen atom or other electron-excess atom, leading to formation of diastereomeric associates.

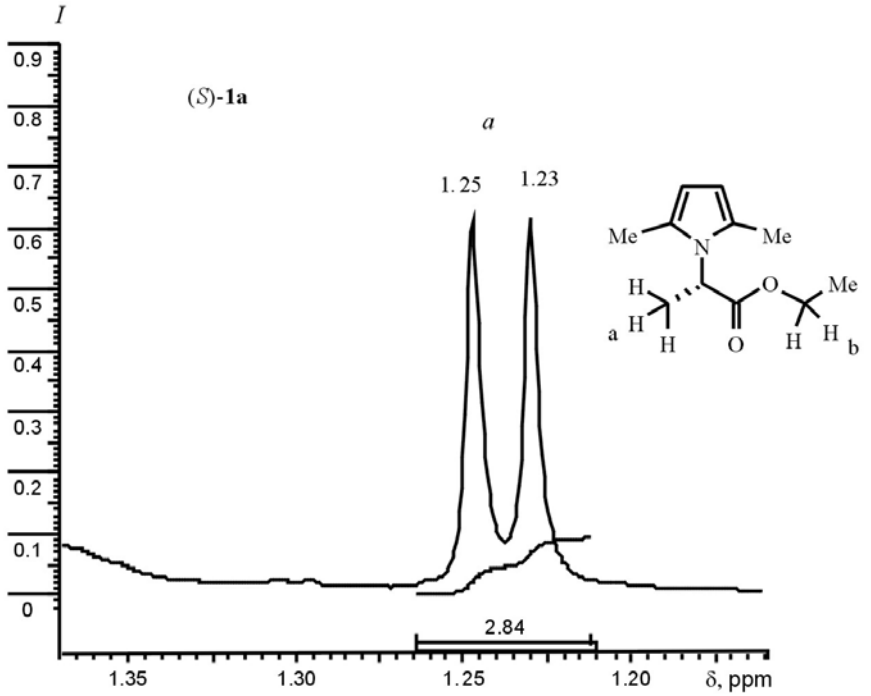
TABLE 1. 2,5-Dimethyl-1H-pyrroles (*S*)-**1a-e** and 5-Aryl-2-methyl-1H-pyrroles (*S*) -**4a-j** with a Chiral Substituent at the Nitrogen Atom

Compound	$[\alpha]^{20}_D$ ($CHCl_3$)	Compound	$[\alpha]^{20}_D$ ($CHCl_3$)	Compound	$[\alpha]^{20}_D$ ($CHCl_3$)
(*S*)-**1a**	+24.2	(*S*)-**4a**	+14.6	(*S*)-**4f**	+19.3
(*S*)-**1b**	+17.8	(*S*)-**4b**	+10.1	(*S*)-**4g**	+14.6
(*S*)-**1c**	+39.6	(*S*)-**4c**	+27.0	(*S*)-**4h**	+36.4
(*S*)-**1d**	+44.9	(*S*)-**4d**	+32.4	(*S*)-**4i**	+41.4
(*S*)-**1e**	+31.4	(*S*)-**4e**	+24.9	(*S*)-**4j**	+28.7

* (*S*)-**1a**,**c**,**d** and (*S*)-**4a–j** *ee* = 98%, (*S*)-**1b**,**e** *ee* = 99%

*Here and subsequently, there was no determination of the absolute configuration for compounds **1** and **4**. The indicated *S*-configuration for compounds**1** and **4** was assigned on the basis of the *S*-configuration of the starting amino acid esters since the chiral site in the key transformation is not affected.


I
(R,S)-1a
a
1.15
1.14
1.13
3.00
Me
N
Me
H
H
a
H
O
O
Me
H
H
b
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.20
1.15
1.10
1.05
1.00
δ, ppm


I
(S)-1a
a
1.25
1.23
2.84
Me
N
Me
H
H
a
H
O
O
Me
H
H
b
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.35
1.30
1.25
1.20
δ, ppm

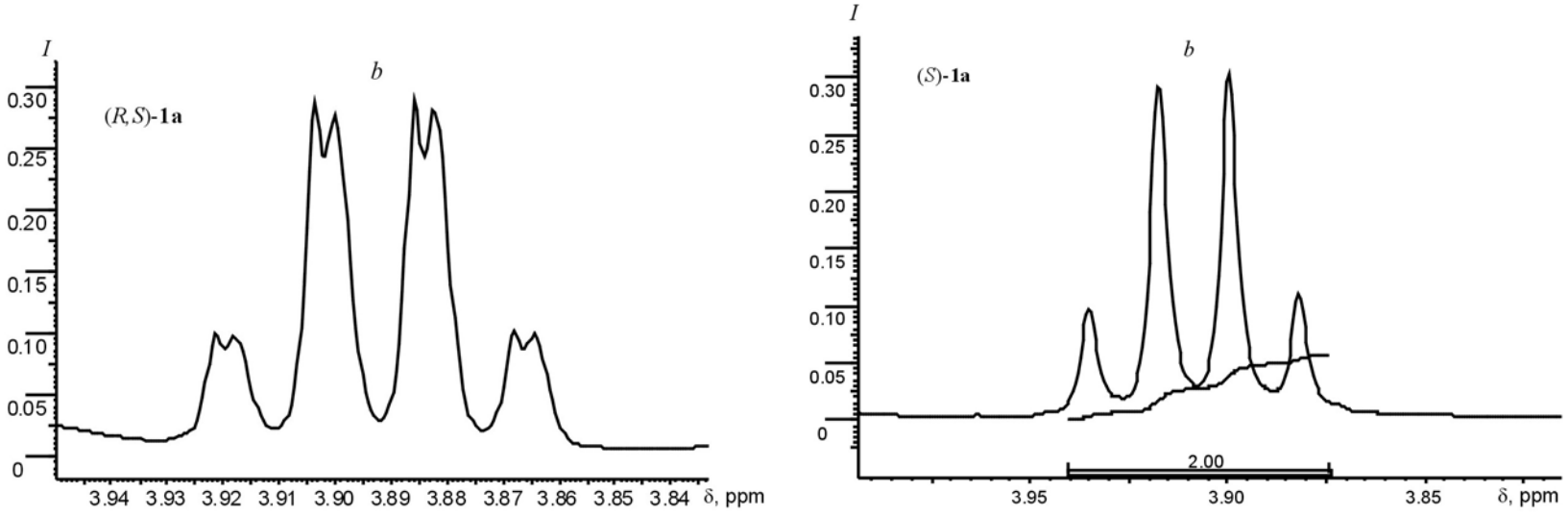


Fig. 1. Fragments of the ^{1}H NMR spectra of ethyl esters (*S*)-**1a** and (*R,S*)-**1a** with (*S*)-1,1'-binaphthyl-2,2'-diol in C_6D_6: *a* – methyl proton signal region and *b* – methylene proton signal region.

TABLE 2. ^{1}H NMR Spectra of Pyrroles **1** and **4***

Com-pound	Chemical shifts ($CDCl_3$), δ, ppm (*J*, Hz)			
	R	CH_3, CH	Pyr, Ph	R^1
1	2	3	4	5
1a	1.61 (3H, d, *J* = 7.0, C<u>H</u>$_3$CH)	2.16 (6H, s, $(CH_3)_2$Pyr); 4.75 (1H, q, *J* = 7.0, CH_3C<u>H</u>)	5.62 (2H, s, H-3,4 Pyr)	1.22 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 4.18-4.24 (2H, m, CH_3C<u>H</u>$_2$)
1b	1.59 (3H, d, *J* = 7.0, C<u>H</u>$_3$CH)	2.16 (6H, s, $(CH_3)_2$Pyr); 4.72 (1H, q, *J* = 7.0, CH_3C<u>H</u>)	5.61 (2H, s, H-3,4 Pyr)	1.41 (9H, s, $(CH_3)_3$C)
1c	0.73 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH); 1.09 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH); 2.29-2.38 (1H, m, $(CH_3)_2$C<u>H</u>)	2.12 (6H, s, $(CH_3)_2$Pyr); 4.07-4.18 (1H, m, CHC<u>H</u>CO_2)	5.72 (2H, s, H-3,4 Pyr)	1.26 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 4.25 (2H, q, *J* = 7.2, CH_3C<u>H</u>$_2$)
1d	3.06 (1H, dd, J_1 = 6.8, J_2 = 3.3, C<u>H</u>$_2$CH); 3.24 (1H, dd, J_1 = 6.8, J_2 = 3.3, C<u>H</u>$_2$CH); 7.04 (2H, d, *J* = 7.6, C_6H_5); 7.24-7.28 (3H, m, C_6H_5)	1.96 (6H, s, $(CH_3)_2$Pyr); 4.60-4.64 (1H, m, CH_2C<u>H</u>)	5.74 (2H, s, H-3,4 Pyr)	1.22 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 4.07-4.16 (2H, m, CH_3C<u>H</u>$_2$)
1e	3.06 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 3.27 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 7.04-7.07 (2H, m, C_6H_5); 7.23-7.27 (3H, m, C_6H_5)	1.90 (6H, s, $(CH_3)_2$Pyr); 4.58-4.62 (1H, m, CH_2C<u>H</u>)	5.74 (2H, s, H-3,4 Pyr)	1.45 (9H, s, $(CH_3)_3$C)
4a	1.61 (3H, d, *J* = 7.0, C<u>H</u>$_3$CH)	2.27 (3H, s, CH_3Pyr); 5.05 (1H, q, *J* = 7.0, CH_3C<u>H</u>)	6.02 (1H, d, *J* = 6.2, H-3 Pyr); 6.13 (1H, d, *J* = 6.2, H-4 Pyr); 7.33-7.46 (5H, m, C_6H_5)	1.24 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 4.80-4.34 (2H, m, CH_3C<u>H</u>$_2$)
4b	1.59 (3H, d, *J* = 7.0, C<u>H</u>$_3$CH)	2.22 (3H, s, CH_3Pyr); 4.99 (1H, q, *J* = 7.0, CH_3C<u>H</u>)	6.00 (1H, d, *J* = 6.2, H-3 Pyr); 6.11 (1H, d, *J* = 6.2, H-4 Pyr); 7.33-7.46 (5H, m, C_6H_5)	1.47 (9H, s, $(CH_3)_3$C)
4c	0.75 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH); 1.16 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH);	2.29 (3H, s, CH_3Pyr); 2.35-2.44 (1H, m, $(CH_3)_2$C<u>H</u>)	6.08 (1H, d, *J* = 6.2, H-3 Pyr); 6.18 (1H, d, *J* = 6.2, H-4 Pyr); 7.33-7.46 (5H, m, C_6H_5)	1.28 (3H, t, *J* = 7.3, C<u>H</u>$_3$CH$_2$); 4.16 (2H, q, *J* = 7.3, CH_3C<u>H</u>$_2$)
4d	3.08 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 3.28 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 7.24-7.28 (3H, m, C_6H_5); 7.04 (2H, d, *J* = 7.6, C_6H_5)	1.96 (3H, s, CH_3Pyr); 4.45-4.49 (1H, m, CH_2C<u>H</u>)	6.14 (1H, d, *J* = 7.7, H-3 Pyr); 6.26 (1H, d, *J* = 7.7, H-4 Pyr); 7.37-7.51 (5H, m, C_6H_5)	1.22 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 4.01-4.06 (2H, m, CH_3C<u>H</u>$_2$)

TABLE 2 (continued)

1	2	3	4	5
4e	3.08 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 3.28 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 7.04 (2H, d, J = 7.7, C_6H_5); 7.24-7.28 (3H, m, C_6H_5)	1.96 (3H, s, CH_3Pyr); 4.43-4.47 (1H, m, CH_2C<u>H</u>)	6.16 (1H, d, J = 7.7, H-3 Pyr); 6.26 (1H, d, J = 7.7, H-4 Pyr); 7.37-7.51 (5H, m , C_6H_5)	1.45 (9H, s, $(CH_3)_3$C)
4f	1.59 (3H, d, J = 7.1, C<u>H</u>$_3$CH)	2.27 (3H, s, CH_3Pyr); 4.98 (1H, q, J = 7.1, CH_3C<u>H</u>)	6.01 (1H, d, J = 6.2, H-3 Pyr); 6.11 (1H, d, J = 6.2, H-4 Pyr); 7.22 (2H, d, J = 7.8, C_6H_4); 7.53 (2H, d, J = 7.8, C_6H_4)	1.28 (3H, t, J = 7.1, C<u>H</u>$_3$CH$_2$); 4.18-4.34 (2H, m, CH_3C<u>H</u>$_2$)
4g	1.56 (3H, d, J = 7.0, C<u>H</u>$_3$CH)	2.22 (3H, s, CH_3Pyr); 4.99 (1H, q, J = 7.0, CH_3C<u>H</u>)	6.00 (1H, d, J = 6.2, H-3 Pyr); 6.11 (1H, d, J = 6.2, H-4 Pyr); 7.21 (2H, d, J = 7.8, C_6H_4); 7.52 (2H, d, J = 7.8, C_6H_4)	1.45 (9H, s, $(CH_3)_3$C)
4h	0.72 (3H, d, J = 7.2, C<u>H</u>$_3$CH); 1.19 (3H, d, J = 7.2, C<u>H</u>$_3$CH)	2.56 (3H, s, CH_3Pyr); 2.81-2.92 (1H, m, $(CH_3)_2$C<u>H</u>)	6.04 (1H, d, J = 6.2, H-3 Pyr); 6.11 (1H, d, J = 6.2, H-4 Pyr); 7.56 (2H, d, J = 7.8, C_6H_4); 7.78 (2H, d, J = 7.8, C_6H_4)	1.56 (3H, t, J = 7.3, C<u>H</u>$_3$CH$_2$); 4.59 (2H, q, J = 7.3, CH_3C<u>H</u>$_2$)
4i	3.08 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 3.28 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 6.84 (2H, d, J = 7.7, C_6H_5); 6.99-7.05 (3H, m, C_6H_5)	2.01 (3H, s, CH_3Pyr); 4.45-4.49 (1H, m, CH_2C<u>H</u>)	6.14 (1H, d, J = 7.7, H-3 Pyr); 6.26 (1H, d, J = 7.7, H-4 Pyr); 7.18 (2H, d, J = 7.8, C_6H_4); 7.39 (2H, d, J = 7.8, C_6H_4)	1.22 (3H, t, J = 7.2, C<u>H</u>$_3$CH$_2$); 4.01-4.06 (2H, m, CH_3C<u>H</u>$_2$)
4j	3.04 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 3.23 (1H, dd, J_1 = 6.8, J_2 = 3.4, C<u>H</u>$_2$CH); 6.80 (2H, d, J = 7.7, C_6H_5); 7.04-7.08 (3H, m, C_6H_5)	1.96 (3H, s, CH_3Pyr); 4.43-4.47 (1H, m, CH_2C<u>H</u>)	6.16 (1H, d, J = 7.7, H-3 Pyr); 6.30 (1H, d, J = 7,7, H-4 Pyr); 7.16 (2H, d, J = 7.8, C_6H_4); 7.38 (2H, d, J = 7.8, C_6H_4)	1.39 (9H, s, $(CH_3)_3$C)

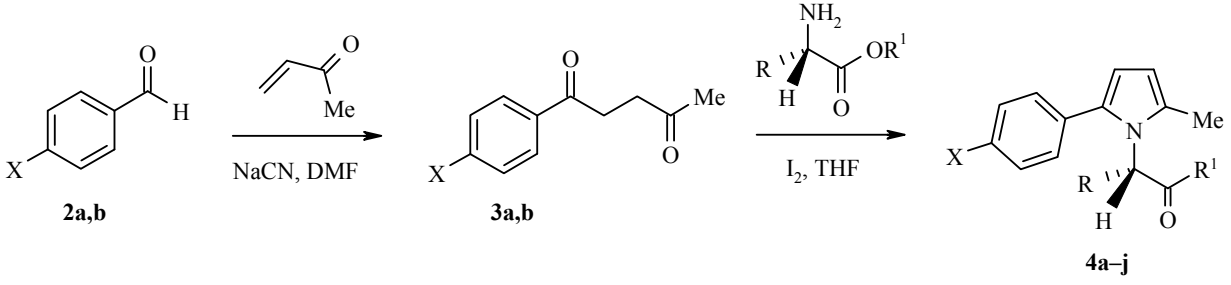
* The spectra of racemic pyrroles are given. The spectra of the corresponding optically active pyrroles are compltely identical to the spectra of the racemates.

The spectrum of compound (*R,S*)-**1a** displays two doublets at 1.13-1.15 ppm with J = 6.8 Hz for both (the distance between the multiplet centers is 2.9 Hz) assigned to $CHC\underline{H}_3$ protons with 1:1 integral intensity (see Fig. 1). The spectrum for compound (*S*)-**1a** shows only one doublet for this group (see Fig. 1). The shape of the multiplet for $C\underline{H}_2CH_3$ protons is evidence for high enantiomeric purity of the sample of compound (*S*)-**1a** obtained upon cyclization of the ethyl ester of alanine under our reaction conditions (Fig. 1).

The optical purity of all the other N-alkyl-2,5-dimethylpyrroles obtained by this method using various amino acids was 98-99% *ee* (Table 1), which suggests that this is a highly stereoselective method for the synthesis of pyrroles with a chiral substituent at the nitrogen atom. The preparative yields of pyrroles **1** are very high (84-90%) (see Experimental).

After developing a method for the cyclization using acetonylacetone, we extended this method for other 1,4-dicarbonyl compounds. Special interest lies in the development of methods for the synthesis of 2-arylpyrroles with a chiral substituent at the nitrogen atom in light of the good prospects for finding new biologically active compounds among such derivatives. Thus, a new class of biologically active compounds was synthesized with atypical neuroleptic (antipsychotic) properties. The antipsychotics have been tested for the treatment of acute mania, acute schizophrenia with excitation, chronic psychoses with behavioral disorder, and aggression. Van Wijngaarden et al. [14] have shown that 2-arylpyrrole derivatives (cyclic analogs of presently used neuroleptics) have higher biological activity than classical neuroleptics such as Haloperidol, Fluanisone, Sulpiride etc. The greatest biological activity was found for 2-arylpyrrole derivatives modified by a tertiary amine or some functional groups of classical antipsychotics. The most common feature of these drugs distinguishing them from classical neuroleptics is a lower D_2-receptors (dopamine receptors) affinity, which are the target for neuroleptics and a multireceptor binding profile. This determines their pharmacological properties, suggesting that these are milder and more readily tolerated drugs with a lower probability of caused extrapyramidal syndrome and other neurological disorders.

Some arylpyrroles display analgesic and anti-inflammatory activity and are bradykinin receptor modulators [15, 16] as well as drugs such as Pyrrolnitrin [17]. However, the 4-aryl-1,4-dicarbonyl compounds required for the preparation of 2-arylpyrroles are unavailable. Hence, we used the Stetter reaction [18], which entails the extensively-studied conjugated addition of benzaldehydes **2a** and **2b** to methyl vinyl ketone catalyzed by cyanide ion for the synthesis of 4-aryl-1,4-dicarbonyl compounds. This reaction proceeds with very high yields reaching 98% [18]. 1,4-Dicarbonyl compounds **3a** and **3b** obtained by the Stetter reaction were used for cyclization with esters of chiral amino acids to give pyrroles by reported methods.



2a,b **3a,b** **4a–j**

2,3 a X = H, **b** X = Br; **4 a–e** X = H, **a** R = Me, R^1 = Et; **b** R = Me, R^1 = *t*-Bu, **c** R = *i*-Pr, R^1 = Et; **d** R = CH_2Ph, R^1 = Et; **e** R = CH_2Ph, R^1 = *t*-Bu; **f,g** X = 4-Br, R = Me, **f** R^1 = Et, **g** R^1 = *t*-Bu; **h–j** X = 4-Br, **h** R = *i*-Pr, R^1 = Et; **i** R = CH_2Ph, R^1 = Et; **j** R = CH_2Ph, R^1 = *t*-Bu

We showed that the structure of the carbonyl compound does not affect either the yields (the yields of 2-methyl-5-phenylpyrroles **4** are 78-87% (see Experimental) nor the stereochemical result (Table 1).

TABLE 3. ^{13}C NMR Spectra of Pyrroles **1** and **4***

Com-pound	Chemical shifts ($CDCl_3$) , δ, ppm
1a	12.05 (2C, 2,5-CH_3); 13.89 (1C, $\underline{C}H_3CH_2$); 19.98 (1C, $\underline{C}H_3CH$); 55.68 (1C, $CH_3\underline{C}H$); 60.84 (1C, $CH_3\underline{C}H_2$); 105.06 (2C, C-3,4 Pyr); 130.97 (2C, C-2,5 Pyr); 175.62 (1C, $\underline{C}O_2Et$)
1b	12.06 (2C, 2,5-CH_3); 20.44 (1C, $\underline{C}H_3CH$); 28.18 (3C, $(\underline{C}H_3)_3C$); 56.40 (1C, $CH_3\underline{C}H$); 80.30 (1C, $(CH_3)_3\underline{C}$); 105.49 (2C, C-3,4 Pyr); 131.88 (2C, C-2,5 Pyr); 176.07 (1C, $\underline{C}O_2Bu$-*t*)
1c	12.09 (2C, 2,5-CH_3); 13.82 (1C, $\underline{C}H_3CH_2$); 19.62 (1C, $\underline{C}H_3CH$); 20.42 (1C, $CH_3\underline{C}H$); 33.11 (1C, $(CH_3)_2\underline{C}H$); 60.44 (1C, $CH_3\underline{C}H_2$); 106.89 (2C, C-3,4 Pyr); 128.05 (2C, C-2,5 Pyr); 175,41 (1C, $\underline{C}O_2Et$)
1d	11.91 (2C, 2,5-CH_3); 14.05 (1C, $\underline{C}H_3CH_2$); 39.27 (1C, $\underline{C}H_2CH$); 59.10 (1C, $CH_2\underline{C}H$); 60.51 (1C, $CH_3\underline{C}H_2$); 106.53 (2C, C-3,4 Pyr); 124.95 (2C, C-2,5 Pyr); 127.21 (1C, C_6H_5); 128.95 (2C, C_6H_5); 129.44 (2C, C_6H_5); 136.24 (1C, C_6H_5); 175.12 (1C, $\underline{C}O_2Et$)
1e	11.94 (2C, 2,5-CH_3); 28.27 (3C, $(\underline{C}H_3)_3C$); 39.21 (1C, $\underline{C}H_2CH$); 59.82 (1C, $CH_2\underline{C}H$); 80.64 (1C, $(CH_3)_3\underline{C}$); 106.53 (2C, C-3,4 Pyr); 125.85 (2C, C-2,5 Pyr); 126.96 (1C, C_6H_5); 128.72 (2C, C_6H_5); 129.21 (2C, C_6H_5); 136.28 (1C, C_6H_5); 174.62 (1C, $\underline{C}O_2Bu$-*t*)
4a	12.29 (1C, 2-CH_3); 13.89 (1C, $\underline{C}H_3CH_2$); 20.26 (1C, $\underline{C}H_3CH$); 55.72 (1C, $CH_3\underline{C}H$); 61.03 (1C, $CH_3\underline{C}H_2$); 107.46 (1C, C-4 Pyr); 109.18 (1C, C-3 Pyr); 126.34 (2C, C_6H_5); 127.97 (2C, C_6H_5); 128.98 (1C, C_6H_5); 131.17 (1C, C_6H_5); 132.16 (1C, C-5 Pyr); 134.43 (1C, C-2 Pyr); 175.08 (1C, $\underline{C}O_2Et$)
4b	12.23 (1C, 2-CH_3); 20.72 (1C, $\underline{C}H_3CH$); 28.27 (3C, $(\underline{C}H_3)_3C$); 56.44 (1C, $CH_3\underline{C}H$); 80.65 (1C, $(CH_3)_3\underline{C}$); 107.46 (1C, C-4 Pyr); 109.18 (1C, C-3 Pyr); 126.34 (2C, C_6H_5); 126.97 (2C, C_6H_5); 128.98 (1C, C_6H_5); 131.92 (1C, C_6H_5); 133.16 (1C, C-5 Pyr); 135.03 (1C, C-2 Pyr); 174.52 (1C, $\underline{C}O_2Bu$-*t*)
4c	13.47 (1C, 2-CH_3); 13.99 (1C, $\underline{C}H_3CH_2$); 20.14 (1C, $\underline{C}H_3CH$); 20.98 (1C, $\underline{C}H_3CH$); 32.90 (1C, $(CH_3)_2\underline{C}H$); 60.62 (1C, $CH_3\underline{C}H_2$); 63.07 (1C, $CH\underline{C}HCO_2$); 106.48 (1C, C-4 Pyr); 110.66 (1C, C-3 Pyr); 127.40 (2C, C_6H_5); 128.03 (2C, C_6H_5); 128.85 (1C, C_6H_5); 131.09 (1C, C_6H_5); 132.30 (1C, C-5 Pyr); 134.32 (1C, C-2 Pyr); 174.86 (1C, $\underline{C}O_2Et$)
4d	12.09 (1C, 2-CH_3); 14.05 (1C, $\underline{C}H_3CH_2$); 39.28 (1C, $\underline{C}H_2CH$); 58.84 (1C, $CH_2\underline{C}H$); 60.70 (1C, $CH_3\underline{C}H_2$); 108.21 (1C, C-4 Pyr); 110.40 (1C, C-3 Pyr); 124.18 (2C, C_6H_5Pyr); 126.96 (1C, C_6H_5); 128.72 (2C, C_6H_5); 128.91 (2C, C_6H_5); 129.61 (1C, C_6H_5Pyr); 130.29 (2C, C_6H_5Pyr); 131.30 (1C, C-2 Pyr); 134.19 (1C, C_6H_5Pyr); 136.86 (1C, C_6H_5); 138.67 (1C, C-5 Pyr); 174.57 (1C, $\underline{C}O_2Et$)
4e	11.97 (1C, 2-CH_3); 28.27 (3C, $(\underline{C}H_3)_3C$); 39.22 (1C, $\underline{C}H_2CH$); 59.56 (1C, $CH_2\underline{C}H$); 80.64 (1C, $(CH_3)_3\underline{C}$); 108.21 (1C, C-4 Pyr); 110.40 (1C, C-3 Pyr); 124.18 (2C, C_6H_5Pyr); 126.96 (1C, C_6H_5); 128.72 (2C, C_6H_5); 128.91 (2C, C_6H_5); 129.61 (1C, C_6H_5Pyr); 130.29 (2C, C_6H_5Pyr); 132.20 (1C, C-2 Pyr); 134.19 (1C, C_6H_5Pyr); 136.90 (1C, C_6H_5); 139.57 (1C, C-5 Pyr); 174.07 (1C, $\underline{C}O_2Bu$-*t*)
4f	12.23 (1C, 2-CH_3); 13.89 (1C, $\underline{C}H_3CH_2$); 20.26 (1C, $\underline{C}H_3CH$); 55.72 (1C, $CH_3\underline{C}H$); 61.03 (1C, $CH_3\underline{C}H_2$); 106.32 (1C, C-4 Pyr); 109.18 (1C, C-3 Pyr); 123.53 (1C, C_6H_4); 125.05 (2C, C_6H_4); 129.47 (2C, C_6H_4); 130.48 (1C, C_6H_4); 132.73 (1C, C-5 Pyr); 134.13 (1C, C-2 Pyr); 175.08 (1C, $\underline{C}O_2Et$)
4g	12.37 (1C, 2-CH_3); 20.72 (1C, $\underline{C}H_3CH$); 28.18 (3C, $(\underline{C}H_3)_3C$); 56.44 (1C, $CH_3\underline{C}H$); 80.65 (1C, $(CH_3)_3\underline{C}$); 106.32 (1C, C-4 Pyr); 109.18 (1C, C-3 Pyr); 123.54 (1C, C_6H_4); 125.31 (2C, C_6H_4); 129.21 (2C, C_6H_4); 130.79 (1C, C_6H_4); 132.98 (1C, C-5 Pyr); 134.36 (1C, C-2 Pyr); 175.19 (1C, $\underline{C}O_2Bu$-*t*)
4h	13.49 (1C, 2-CH_3); 14.29 (1C, $\underline{C}H_3CH_2$); 19.25 (1C, $\underline{C}H_3CH$); 20.28 (1C, $\underline{C}H_3CH$); 32.90 (1C, $(CH_3)_2\underline{C}H$); 60.65 (1C, $CH_3\underline{C}H_2$); 63.07 (1C, $CH\underline{C}HCO_2$); 105.34 (1C, C-4 Pyr); 110.66 (1C, C-3 Pyr); 123.40 (1C, C_6H_4); 128.80 (2C, C_6H_4); 129.87 (2C, C_6H_4 30.88 (1C, C_6H_4); 132.73 (1C, C-5 Pyr); 134.89 (1C, C-2 Pyr); 174.89 (1C, $\underline{C}O_2Et$)
4i	12.13 (1C, 2-CH_3); 14.18 (1C, $\underline{C}H_3CH_2$); 39.68 (1C, $\underline{C}H_2CH$); 58.84 (1C, $CH_2\underline{C}H$); 60.70 (1C, $CH_3\underline{C}H_2$); 108.21 (1C, C-4 Pyr); 110.40 (1C, C-3 Pyr); 124.18 (2C, C_6H_4); 126.96 (1C, C_6H_5); 128.72 (2C, C_6H_5); 128.91 (2C, C_6H_5); 129.61 (1C, C_6H_4); 130.29 (2C, C_6H_4); 131.30 (1C, C-2 Pyr); 134.19 (1C, C_6H_4); 136.86 (1C, C_6H_5); 138.67 (1C, C-5 Pyr); 174.57 (1C, $\underline{C}O_2Et$)
4j	12.09 (1C, 2-CH_3); 28.27 (3C, $(\underline{C}H_3)_3C$); 39.22 (1C, $\underline{C}H_2CH$); 59.56 (1C, $CH_2\underline{C}H$); 80.64 (1C, $(CH_3)_3\underline{C}$); 108.21 (1C, C-4 Pyr); 110.40 (1C, C-3 Pyr); 124.18 (2C, C_6H_4); 126.96 (1C, C_6H_5); 128.72 (2C, C_6H_5); 128.91 (2C, C_6H_5); 129.61 (1C, C_6H_4); 130.29 (2C, C_6H_4); 131.30 (1C, C-2 Pyr); 134.19 (1C, C_6H_4) 136.86 (1C, C_6H_5); 138.67 (1C, C-5 Pyr); 174.57 (1C, $\underline{C}O_2Bu$-*t*)

* The spectra of racemic pyrroles are given. The spectra of the corresponding optically active pyrroles are compltely identical to the spectra of the racemates

Thus, we propose a new and efficient approach for the preparation of optically active pure pyrroles with a chiral substituent at the nitrogen atom based on the Paal-Knorr reaction using iodine as the cyclization catalyst and esters of (*S*)-amino acids as the sources of chirality.

EXPERIMENTAL

The IR spectra were taken for vaseline mulls on a UR-20 spectrometer. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker Avance-400 spectrometer at 400 and 100 MHz, respectively, with TMS as the internal standard. The mass spectra were taken on a Finnigan MAT mass spectrometer using electron impact ionization and an ITD-700 detector. The ionizing electron energy was 70 eV and the mass range was *m/z* 35-400. The specific rotation was measured on Perkin-Elmer 241 and Jasco DIP-360 polarimeters at 589 nm in cells with path length 5 and 10 cm. Methylene chloride, chloroform, and methanol were used as the solvent for measurement of the specific rotation. The GC/MS study was carried out using an Agilent 1200 gas-liquid chromatograph with fluorimetric and diode-matrix detectors, a 4.6×250 mm Chiralcel OD-H column, detection at UV 250 nm, and 95:5 hexane–2-propanol as the mobile phase. The flow rate was 1 ml/min. The melting points were measured in open capillaries and presented without correction.

2,5-Disubstituted N-Alkylpyrroles 1a-e and 4a-j (General Method). A. Triethylamine (1.4 ml, 0.01 mol) was added to a solution of hydrochloride salt of the amino acid ester (0.01 mol) in THF (10 ml) and stirred for 30 min at room temperature. Then, 1,4-dicarbonyl compound (0.012 mol) and iodine (0.254 g, 0.001 mol) were added. The reaction mixture was stirred for 24 h at room temperature and then poured into 200 ml methylene chloride. The organic layer was washed with 100 ml 0.1 N aqueous sodium thiosulfate and, then, 100 ml 0.5 mol/liter aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed in vacuum. The residue was subjected to chromatography on a silica gel column using 50:1 petroleum ether–ethyl acetate as the eluent.

B. Acetonylacetone (1.41 ml, 0.012 mol) and iodine (0.254 g, 0.001 mol) were added to a solution of amino acid ester (0.01 mol) in THF (10 ml). The reaction was carried out and the reaction mixture was worked up analogously to method A.

The ^{1}H and ^{13}C NMR spectral data for pyrroles **1** and **4** are given in Tables 2 and 3.

Ethyl Ester of 2-(2,5-Dimethyl-1H-pyrrol-1-yl)propionic Acid (*R,S*)-(1a) was obtained as an oil in 88% (method A) and 61% yield (method B). IR spectrum*, ν, cm^{-1}: 2920, 1750. Mass spectrum*, *m/z* (I_{rel}, %): 195 $[M]^+$ (32), 122 (100), 94 (66), 79 (15), 53 (16), 42 (15.8), 41 (13). Found, %: C 67.83; H 8.91; N 7.32. $C_{11}H_{17}NO_2$. Calculated, %: C 67.66; H 8.71; N 7.17.

Ethyl Ester (2*S*)-(1a) was obtained in 92% yield (method A). Found, %: C 67.71; H 8.80; N 7.20. $C_{11}H_{17}NO_2$. Calculated, %: C 67.66; H 8.71; N 7.17.

***tert*-Butyl Ester of 2-(2,5-Dimethyl-1H-pyrrol-1-yl)propionic Acid (*R,S*)-(1b)** was obtained as an oil in 85% (method A) and 54% yield (method B). IR spectrum, ν, cm^{-1}: 2925, 1744. Mass spectrum, *m/z* (I_{rel}, %): 223 $[M]^+$ (32), 122 (100), 94 (66), 79 (15), 57 (97), 53 (16), 42 (16), 41 (64). Found, %: C 69.99; H 9.67; N 6.34. $C_{13}H_{21}NO_2$. Calculated, %: C 69.92; H 9.48; N 6.27.

***tert*-Butyl Ester (2*S*)-1b** was obtained in 87% yield (method A). Found, %: C 69.84; H 9.53; N 6.30. $C_{13}H_{21}NO_2$. Calculated, %: C 69.92; H 9.48; N 6.27.

Ethyl Ester of 2-(2,5-Dimethyl-1H-pyrrol-1-yl)-3-methylbutanoic Acid (*R,S*)-(1c) was obtained as an oil in 86% (method A) and 60% yield (method B). IR spectrum, ν, cm^{-1}: 2920, 1740. Mass spectrum, *m/z* (I_{rel}, %):

*The IR and mass spectra taken for the optically active pyrroles were identical to the spectra of the corresponding racemic samples.

223 $[M]^+$ (57), 150 (77), 108 (73), 96 (28), 95 (47), 94 (100), 55 (20), 53 (21), 43 (31), 42 (23), 41 (37), 39 (25). Found, %: C 69.83; H 9.61; N 6.32. $C_{13}H_{21}NO_2$. Calculated, %: C 69.92; H 9.48; N 6.27

Ethyl Ester (*S*)-(1c) was obtained in 90% yield (method A). Found, %: C 69.88; H 9.52; N 6.29. $C_{13}H_{21}NO_2$. Calculated, %: C 69.92; H 9.48; N 6.27.

Ethyl Ester of 2-(2,5-Dimethyl-1H-pyrrol-1-yl)-3-phenylpropionic Acid (*R,S*)-(1d) was obtained as an oil in 84% (method A) and 60% yield (method B). IR spectrum, ν, cm^{-1}: 2940, 1745. Mass spectrum, *m/z* (I_{rel}, %): 271 $[M]^+$ (16), 198 (76), 108 (53), 106 (22), 95 (53), 94 (92), 91 (100), 77 (36), 65 (23), 53 (25), 42 (20). Found, %: C 75.43; H 7.91; N 5.32. $C_{17}H_{21}NO_2$. Calculated, %: C 75.25; H 7.80; N 5.16.

Ethyl Ester (*S*)-(1d) was obtained in 89% yield (method A). Found, %: C 75.32; H 7.97; N 5.25. $C_{17}H_{21}NO_2$. Calculated, %: C 75.25; H 7.80; N 5.16.

***tert*-Butyl Ester of 2-(2,5-Dimethyl-1H-pyrrol-1-yl)-3-phenylpropionic Acid (*R,S*)-(1e)** was obtained as an oil in 84% (method A) and 51% yield (method B). IR spectrum, ν, cm^{-1}: 2940, 1745. Mass spectrum, *m/z* (I_{rel}, %): 299 $[M]^+$ (67), 198 (76), 131 (21), 108 (53), 106 (22), 95 (52), 94 (92), 91 (100), 79 (20), 77 (36), 65 (23), 57 (84), 41 (81). Found, %: C 76.08; H 8.67; N 4.64. $C_{19}H_{25}NO_2$. Calculated, %: C 76.22; H 8.42; N 4.68.

***tert*-Butyl eEster (*S*)-(1e)** was obtained in 87% yield (method A). Found, %: C 76.19; H 8.54; N 4.70. $C_{19}H_{25}NO_2$. Calculated, %: C 76.22; H 8.42; N 4.68.

Preparation of 1,4-Dicarbonyl Compounds from Benzaldehydes (General Method). A solution of freshly distilled benzaldehyde **2a** or **2b** (0.1 mol) and anhydrous DMF (50 ml) was added dropwise over 10 min to a mixture of sodium cyanide (0.49 g, 0.01 mol) and anhydrous DMF (50 ml) at 35°C. The reaction mixture was maintained at this temperature for 15 min. Then, a solution of freshly distilled methyl vinyl ketone (5.3 g, 0.075 mol) in anhydrous DMF (100 ml) was added dropwise over 20 min. The reaction mixture was maintained for 2 h at 35°C, poured into 300 ml water, and extracted with three 150-ml methylene chloride portions. The organic phase was washed with 150 ml 0.5 mol/l aqueous hydrochloric acid, aqueous sodium bicarbonate (150 ml, 0.5 mol/l), and three 150-ml water portions and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum. The residue was subjected to chromatography on a silica gel column using 10:1 petroleum ether–ethyl acetate as the eluent.

1-Phenylpentane-1,4-dione (3a) was obtained in 82% yield; mp 125-126°C (133 Pa) (bp 128-129°C (133 Pa) [19]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.12 (3H, s, CH_3CO); 2.58 (2H, t, *J* = 5.4, $C\underline{H}_2COMe$); 3.06 (2H, t, *J* = 5.4, $C\underline{H}_2COPh$); 7.45-7.52 (2H, m, C_6H_5); 8.11-8.17 (3H, m, C_6H_5).

1-(4-Bromophenyl)pentane-1,4-dione (3b) was obtained in 96% yield, mp 84°C (petroleum ether) (mp 86°C (from petroleum ether) [19]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.15 (3H, s, CH_3CO); 2.56 (2H, t, *J* = 5.4, $C\underline{H}_2COMe$); 3.07 (2H, t, *J* = 5.4, $C\underline{H}_2COPh$); 7.44 (2H, d, *J* = 7.8, C_6H_4); 7.89 (2H, d, *J* = 7.8, C_6H_4).

Ethyl Ester of 2-(2-Methyl-5-phenyl-1H-pyrrol-1-yl)propionic Acid (*R,S*)-(4a) was obtained as an oil in 81% (method A) and 58% yield (method B). IR spectrum, ν, cm^{-1}: 2954, 1750, 1435, 1352, 1160. Mass spectrum, *m/z* (I_{rel}, %): 257 $[M]^+$ (15), 256 (85), 185 (18), 184 (100), 156 (99), 128 (27), 115 (23), 77 (16). Found, %: C 74.89; H 7.31; N 5.32. $C_{16}H_{19}NO_2$. Calculated, %: C 74.68; H 7.44; N 5.44.

Ethyl Ester (*S*)-(4a) was obtained in 85% yield (method A). Found, %: C 74.72; H 7.39; N 5.40. $C_{16}H_{19}NO_2$. Calculated, %: C 74.68; H 7.44; N 5.44.

***tert*-Butyl Ester of 2-(2-Methyl-5-phenyl-1H-pyrrol-1-yl)butanoic Acid (*R,S*)-(4b)** was obtained as an oil in 82% (method A) and 56% yield (method B). IR spectrum, ν, cm^{-1}: 2960, 1750, 1435, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 285 $[M]^+$ (22), 284 (85), 185 (18), 184 (98), 156 (88), 128 (27), 115 (22), 77 (16), 57 (100), 41 (64). Found, %: C 75.59; H 8.01; N 4.92. $C_{18}H_{23}NO_2$. Calculated, %: C 75.76; H 8.12; N 4.91.

***tert*-Butyl Ester (*S*)-(4b)** was obtained in 87% yield (method A). Found, %: C 75.68; H 8.10; N 4.90. $C_{18}H_{23}NO_2$. Calculated, %: C 75.76; H 8.12; N 4.91.

Ethyl Ester of 3-Methyl-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)butanoic Acid (*R,S*)-(4c) was obtained as an oil in 80% (method A) and 59% yield (method B). IR spectrum, ν, cm^{-1}: 2975; 1768, 1437, 1350, 1160. ass spectrum, *m/z* (I_{rel}, %): 285 $[M]^+$ (16), 212 (59), 170 (42), 168 (22), 157 (58), 156 (100), 115 (23), 55 (21), 43 (35), 41 (32). Found, %: C 75.63; H 8.01; N 5.02. $C_{18}H_{23}NO_2$. Calculated, %: C 75.76; H 8.12; N 4.91.

Ethyl Ester (*S*)-(4c) was obtained in 80% yield (method A). Found, %: C 75.71; H 8.17; N 5.00. $C_{18}H_{23}NO_2$. Calculated, %: C 75.76; H 8.12; N 4.91.

Ethyl Ester of 2-(2-Methyl-5-phenyl-1H-pyrrol-1-yl)-3-phenylpropionic Acid (*R,S*)-(4d) was obtained as an oil in 78% (method A) and 52% yield (method B). IR spectrum, ν, cm^{-1}: 2980, 1770, 1440, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 333 $[M]^+$ (26), 332 (84), 260 (100), 170 (23), 169 (38), 168 (64), 157 (58), 156 (92), 115 (29), 105 (51), 91 (82), 77 (48). Found, %: C 79.43; H 6.91; H 4.32. $C_{22}H_{23}NO_2$. Calculated, %: C 79.25; H 6.95; N 4.20.

Ethyl Ester (*S*)-(4d) was obtained in 82% yield (method A). Found, %: C 79.34; H 6.89; N 4.26. $C_{22}H_{23}NO_2$. Calculated, %: C 79.25; H 6.95; N 4.20.

***tert*-Butyl Ester of 2-(2-Methyl-5-phenyl-1H-pyrrol-1-yl)-3-phenylpropionic Acid (*R,S*)-(4e)** was obtained as an oil in 81% (method A) and 50% yield (method B). IR spectrum, ν, cm^{-1}: 2980, 1770, 1440, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 361 $[M]^+$ (84), 260 (100), 169 (38), 168 (64), 157 (58), 156 (73), 115 (29), 105 (51), 91 (83), 77 (48), 65 (23), 57 (100), 51 (29), 41 (59). Found, %: C 79.63; H 7.41; N 3.72. $C_{24}H_{27}NO_2$. Calculated, %: C 79.74; H 7.53; N 3.87.

***tert*-Butyl Ester (*S*)-(4e)** was obtained as an oil in 85% yield (method B). Found: C 79.70; H 7.57; N 3.83%. $C_{24}H_{27}NO_2$. Calculated, %: C 79.74; H 7.53; N 3.87.

Ethyl Ester of 2-[2-(4-Bromophenyl)-5-methyl-1H-pyrrol-1-yl]propionic Acid (*R,S*)-(4f) was obtained as an oil in 83% (method A) and 60% yield (method B). IR spectrum, ν, cm^{-1}: 3080, 2955, 1757, 1440, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 337 $[M]^+$ (26), 335 $[M]^+$ (28), 264 (97), 262 (100), 183 (34), 155 (58), 75 (65), 63 (49), 41 (37). Found, %: C 57.29; H 5.31; N 4.32. $C_{16}H_{18}BrNO_2$. Calculated, %: C 57.16; H 5.40; N 4.17.

Ethyl Ester (*S*)-(4f) was obtained in 87% yield (method A). Found, %: C 57.18; H 5.37; N 4.23. $C_{16}H_{18}BrNO_2$. Calculated, %: C 57.16; H 5.40; N 4.17.

***tert*-Butyl Ester of 2-[2-(4-Bromophenyl)-5-methyl-1H-pyrrol-1-yl]propionic Acid (*R,S*)-(4f)** was obtained as an oil in 81% (method A) and 57% yield (method B). IR spectrum, ν, cm^{-1}: 3080, 2965, 1760, 1450, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 365 $[M]^+$ (29), 363 (29), 264 (37), 262 (39), 170 (18), 168 (64), 157 (58), 156 (73), 115 (29), 105 (51), 91 (83), 77 (48), 65 (23), 57 (100), 51 (29), 41 (54), 39 (16). Found,%: C 59.19; H 6.01; N 3.92. $C_{18}H_{22}BrNO_2$. Calculated, %: C 59.35; H 6.09; N 3.85.

***tert*-Butyl Ester (*S*)-(4f)** was obtained in 81% yield (method B). Found, %: C 59.27; H 6.07; N 3.84. $C_{18}H_{22}BrNO_2$. Calculated, %: C 59.35; H 6.09; N 3.85.

Ethyl Ester of 2-[2-(4-Bromophenyl)-5-methyl-1H-pyrrol-1H-yl]-3-methylbutanoic Acid (*R,S*)-(4h) was obtained as an oil in 80% (method A) and 53% (method B). IR spectrum, ν, cm^{-1}: 3083, 2955, 1757, 1440, 1350, 1160. Mass spectrum, *m/z* (I_{rel}, %): 365 $[M]^+$ (86), 363 $[M]^+$ (87), 292 (28), 290 (28), 250 (32), 240 (32), 236 (97), 234 (100), 168 (54), 166 (33), 155 (31), 141 (22), 128 (26), 115 (35), 55 (34), 53 (26), 43 (55). Found, %: C 59.23; H 6.01; N 3.96. $C_{18}H_{22}BrNO_2$. Calculated, %: C 59.35; H 6.09; N 3,85.

Ethyl Ester (*S*)-(4h) was obtained in 80% yield (method A). Found, %: C 59.37; H 6.06; N 3.89. $C_{18}H_{22}BrNO_2$. Calculated, %: C 59.35; H 6.09; N 3.85.

Ethyl Ester of 2-[2-(4-Bromophenyl)-5-methyl-1H-pyrrol-1-yl]-3-phenylpropionic Acid (*R,S*)-(4i) was obtained as an oil in 78% (method A) and 52% yield (method B). IR spectrum, ν, cm^{-1}: 3080, 2970, 1765, 1450, 1365, 1160. Mass spectrum, *m/z* (I_{rel}, %): 413 $[M]^+$ (34), 411 $[M]^+$ (39), 340 (86), 338 (87), 236 (54), 234 (53), 169 (22), 167 (36), 155 (20), 115 (24), 91 (100), 77 (30), 65 (20). Found, %: C 64.23; H 5.41; N 3.42. $C_{22}H_{22}BrNO_2$. Calculated, %: C 64.09; H 5.38; N 3.40.

Ethyl Ester (*S*)-(4i) was obtained in 82% yield (method A). Found, %: C 64.17; H 5.43; N 3.41. $C_{22}H_{22}BrNO_2$. Calculated, %: C 64.09; H 5.38; N 3.40.

***tert*-Butyl Ester of 2-[2-(4-Bromophenyl)-5-methyl-1H-pyrrol-1-yl]-3-phenylpropionic Acid (*R*,*S*)-(4j)** was obtained as an oil in 79% (method A) and 54% yield (method B). IR spectrum, ν, cm^{-1}: 3080, 2970, 1765, 1450, 1365, 1160. Mass spectrum, *m/z* (I_{rel}, %): 441 $[M]^+$ (42), 439 $[M]^+$ (41), 340 (32), 338 (33), 236 (54), 234 (53), 169 (32), 167 (36), 155 (20), 115 (24), 105 (21), 103 (26), 91 (100), 43 (54). Found, %: C 65.32; H 5.91; N 3.24. $C_{24}H_{26}BrNO_2$. Calculated, %: C 65.46; H 5.95; N 3.18.

***tert*-Butyl Ester (*S*)-4j)** was obtained in 78% yield (method B). Found, %: C 65.41; H 5.90; N 3.16. $C_{24}H_{26}BrNO_2$. Calculated, %: C 65.46; H 5.95; N 3.18.

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